Insulin-Like Growth Factors, Insulin-Like Growth Factor-Binding Proteins, and Endometrial Cancer in Postmenopausal Women: Results from a U.S. Case-Control Study

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Abstract

Objective: To assess whether circulating insulin-like growth factor-1 (IGF-1), IGF-2, insulin-like growth factor-binding protein-1 (IGFBP-1), or IGFBP-3 were associated with endometrial cancer in postmenopausal women. Study Design: Between 1987 and 1990, we conducted a case-control study of 405 women with endometrial cancer and 297 matched population-based controls. This analysis included 174 postmenopausal cases and 136 controls. Results: In logistic regression models adjusted for potential confounders, higher IGF-1 levels were not positively associated with endometrial cancer: odds ratio (OR) for the highest tertile *versus* the lowest tertile = 0.63, 95% confidence interval (CI) = 0.30–1.32. Endometrial cancer was inversely associated with IGF-2 (OR for the highest tertile = 0.35, 95% CI = 0.18–0.69) and IGFBP-3 (OR for the highest tertile = 0.40, 95% CI = 0.21–0.77), and not associated with IGFBP-1. Conclusion: Serum IGF-1, IGF-2, and IGFBP-3, but not IGFBP-1, were inversely associated with endometrial cancer in postmenopausal women. These associations and the potential role of the IGF system in endometrial proliferation and carcinogenesis warrant further research. (Cancer Epidemiol Biomarkers Prev 2004;13(4):607–612)

Introduction

The ''unopposed estrogen'' theory, in which excess estrogen in the presence of insufficient progesterone promotes carcinogenesis, incorporates a majority of the epidemiological and experimental data on known endometrial cancer risk factors (1). Whether elevated estrogen exposure or depressed progesterone levels—or both—plays the key role is unclear, but exogenous factors that contribute to one or the other, such as oral contraceptives or menopausal estrogens, have been associated with endometrial cancer risk (2). Higher circulating levels of endogenous estrone (3–5), estradiol (4, 5), and androstenedione (3) have been associated with an increased endometrial cancer risk, but the extent to which other hormone-related exposures, particularly obesity, are similarly associated has not been resolved (4, 6).

Within endometrial tissue, insulin-like growth factor-1 (IGF-1) may mediate the proliferative effects of estrogen (7). IGF-1 is a member of the IGF family, which includes IGF-1 and IGF-2, their receptors (IGF-1R and IGF-2R), and at least six binding proteins (IGFBP-1 through IGFBP-6) (8). IGF-1 and IGF-2 are potent mitogens and have anti-apoptotic properties, whereas the IGFBPs tend to reduce the amount of bioavailable IGFs and counteract their proliferative actions. Higher levels of IGF-1 have been associated with an increased risk of a number of epithelial cancers (9), and correlations between higher estrogen levels and IGF-1 expression and between higher progesterone levels and IGFBP-1 levels provide a potential link between the IGF system, the estrogen-progesterone balance, and endometrial cancer risk (10, 11).

Until recently, the available data on IGFs, IGFBPs, and endometrial cancer consisted almost exclusively of small clinic-based investigations (12, 13). Primarily null associations, but a few potential positive associations, appeared in three case-control studies that examined IGFs and IGFBPs. The study of Petridou *et al.* (14) showed positive and inverse associations with IGF-2 and IGF-1, respectively, whereas the results of Weiderpass *et al.* (15) were null except for a potential positive

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association with IGFBP-1 among women who never used menopausal hormone therapy. The nested case-control study from Lukanova *et al.* (16), using data from three cohorts, reported an inverse association with IGFBP-1, but no associations with IGF-1, IGFBP-2, or IGFBP-3. To provide additional data with which to assess these inconsistencies, we evaluated IGFs and IGFBPs in a multicenter U.S. endometrial cancer case-control study, which has previously provided information on risk associated with endogenous hormones (3), obesity (6), C-peptide (17), and other risk factors (18–20).

Methods

Study Population. This previously described study (18) included 20- to 74-year-old women who were diagnosed with pathologically confirmed endometrial cancer between June 1987 and May 1990 at seven U.S. referral hospitals [Chicago (Northwestern University), IL; Chicago (Rush Medical College), IL; Hershey, PA; Irvine, CA; Long Beach, CA; Minneapolis, MN; and Winston-Salem, NC]. Random digit dialing (RDD) identified age-, race-, and location-matched (*i.e.*, in the same residential telephone exchange as their index case) controls for younger (<65 years) cases, while random selection from Health Care Financing Administration (HCFA) files, matched on residential zip code, identified similarly matched controls for older (≥65 years) cases.

All potential controls completed a short questionnaire to ascertain hysterectomy status; additional eligible potential controls replaced women who reported a hysterectomy. Because we identified the cases from referral hospitals and used community-based controls, we included a second control group to potentially improve the comparability with the case patients. Women who were having a hysterectomy for benign conditions at the seven referral centers were matched on age, race, and location to cases; as necessary, matching criteria, especially age, were relaxed. Uterine leiomyoma (63%) was the most common primary diagnosis for postmenopausal hysterectomy control subjects (3). Home interviews were obtained for 434 of 498 eligible cases (87.1%), 313 of 477 eligible community controls (65.6%; n = 304 from RDD and n = 173 from HCFA), and 206 of 253 eligible hysterectomy controls (81.4%).

Institutional review boards at NCI and each clinic approved this study.

Blood Collection. We collected fasting blood samples from cases and hysterectomy controls before their surgeries, and from community controls, usually within 1 month of their interviews. Of the 434 interviewed cases, 325 (74.9%) donated blood samples. Of the 519 total interviewed controls, 356 (68.6%) donated blood samples. We excluded samples from 49 case women and 39 control women who reported exogenous estrogen or oral contraceptive use within 6 months of blood draw, and from 1 control woman who was pregnant at the time of blood draw.

Laboratory Analysis. This analysis followed a number of previous laboratory analyses from this study population, and therefore no sera remained for 33 cases, 34 community controls, and 3 hysterectomy controls. We excluded these participants. To focus on postmenopausal women, in whom endometrial cancer rates are highest and the role of endogenous hormones can be most clearly studied, we excluded premenopausal women (68 cases, 53 community controls, and 54 hysterectomy controls).

We shipped sera to Diagnostic Systems Laboratories (DSL; Webster, TX), who used ELISA to analyze samples in case-control pairs masked to case status. In each batch of 36 samples, we inserted four blinded quality surveillance specimens to monitor assay quality. We obtained these quality control samples from three individuals who were expected to cover the low, medium, and high range of IGFs levels.

DSL measured IGF-1, IGF-2, IGFBP-1, and IGFBP-3 twice for each sample and re-assayed samples if the duplicate measures differed by more than 10%. We used the mean value for all statistical analysis. We also excluded 1 case, 13 community controls, and 2 hysterectomy controls because of ambiguities in specimen identification.

Statistical Analysis. We excluded the 21 hysterectomy controls who reportedly had endometrial hyperplasia and therefore may have been at increased risk for endometrial cancer (21). Mean IGF levels were substantially lower among the hysterectomy controls with hyperplasia than among the hysterectomy controls without endometrial hyperplasia and among the community controls (data not shown). The final analytic data set included 174 postmenopausal cases and 136 controls (98 community controls and 38 hysterectomy controls; Table 1).

Because this analysis included a subset of the full study, which was individually matched, use of adjusted unconditional logistic regression rather than conditional models allowed us to generate odds ratios (ORs) and confidence intervals (CIs) without sacrificing all discordant case-control pairs. The distribution of IGFs and IGFBPs among controls formed the basis of tertile cutpoints. For IGFs and IGFBPs, ORs reflect associations based on the lowest tertile as the reference category. We assessed recognized and hypothesized endometrial cancer risk factors as potential confounders but chose a final model that included age (<55, 55–59, 60–64, or ≥65 years), race (non-Hispanic white *versus* all other), study site [Chicago (Northwestern), IL; Chicago (Rush), IL; Hershey, PA; Irvine, CA; Long Beach, CA; Minneapolis, MN; or Winston-Salem, NC], body mass index (BMI,

Table 1. Study population and reasons for exclusion[a]

	Cases	Controls
No. eligible	498	730
No. interviewed	434	519
No. donated blood	325	356
Reasons for exclusion		
Exogenous hormone use or pregnant at blood draw	49	40
Insufficient serum	33	37
Premenopausal	68	107
ID discrepancy during IGF analysis	1	15
Analytic population	174	157
Hyperplasia at time of blood draw	0	21
Final analytic population	174	136

[a]See "Methods."

calculated as kg/m^2; <23.19, 23.19–26.83, or >26.83 kg/m^2), and sex-hormone binding globulin (on a log scale; <3.53, 3.53–4.05, or ≥4.06 nM/L). Additional adjustment for factors such as serum hormones, smoking, duration of menopausal estrogen use, or C-peptide levels did not appreciably change the results, and therefore we present only the parsimonious final models.

Results

Table 2 shows selected descriptive factors for the analytic population. Although this population slightly differed from the study population reported in previous publications, the main risk factor associations were essentially identical to earlier analyses. Increasing parity (OR = 0.55 for three or more pregnancies), current smoking (OR = 0.37), higher log serum SHBG levels (OR = 0.27 for ≥4.06 nM), and higher serum cholesterol levels (OR = 0.53 for ≥256 mg/dl) were inversely associated while increasing duration of menopausal estrogen use (OR = 6.27 for ≥60 months), higher BMI (OR = 3.63 for ≥26.84 kg/m^2), higher waist-to-thigh ratio (OR = 3.58 for ≥1.915), higher log androstenedione levels (OR = 2.64 for ≥4.37 ng/dl), and higher log albumin-bound estradiol (OR = 3.08 for ≥0.77 pg/ml) were positively associated with endometrial cancer in analyses adjusted for study site, age, and race. As in a previous study analysis, a positive association with higher serum C-peptide levels (OR = 2.22 for ≥2.3 ng/ml) in models adjusted for study matching factors disappeared after additional adjustment for BMI and SHBG levels (OR = 0.75, 95% CI, 0.34–1.66).

The excluded participants differed from the included participants on a number of factors. Excluded women were significantly younger and less likely to have used menopausal estrogen therapy (although over 85% of the total study population had never used estrogen therapy), and had significantly higher levels of serum estrogens and androgens. However, the questionnaire risk factor ORs from logistic regression analyses restricted to the excluded participants did not substantially differ from the ORs from the same models using only the included participants [*e.g.*, the OR for BMI in highest tertile was 2.34 (95% CI, 1.28–4.30) among excluded women]. The ORs for the serum hormones also did not substantially differ in models restricted to excluded participants: the OR for the highest tertile of androstenedione was 2.15 (95% CI, 0.88–5.24), the OR for the highest tertile of bioavailable estradiol was 4.14 (95% CI, 1.54–11.12), and the OR for the highest tertile of SHBG was 0.37 (95% CI, 0.19–0.69).

Mean levels (and interquartile ranges) in cases *versus* controls for IGF-1, IGF-2, IGFBP-1, and IGFBP-3 were 94.02 ng/ml (57.25–125.7) *versus* 102.98 ng/ml (67.75–122.20); 622.31 ng/ml (475.85–743.60) *versus* 694.89 ng/ml (532.63–809.53); 44.4 ng/ml (15.6–57.0) *versus* 51.3 ng/ml (24.0–71.2); and 3295.55 ng/ml (2610.00–3845.00) *versus* 3683.38 ng/ml (3025.25 – 4219.50), respectively. The coefficients of variation (CV), taking into account intra- and inter-assay variability, for IGF-1, IGF-2, IGFBP-1, and IGFBP-3 were 50%, 12.9%, 10.1%, and 10%, respectively. The mean IGF-1 levels among the QC samples in the first two batches—270.62 ng/ml among cases and 308.28 ng/ml among controls—were approximately 3 times higher than the mean IGF-1 levels among the QC samples in the other batches. After excluding these two batches, the CV for IGF-1 was 12.9%. We therefore excluded all batch 1 and batch 2 results for the IGF-1 analysis only (a total of 31 cases and 28 controls). One additional case and 4 more controls had missing IGF-1 data. For the IGF-1 models, these exclusions generated empty cells in some study site strata and led us to combine two study sites (MN and NC) into one in multivariate regression models.

ORs for the second and third tertiles of IGF-1 were below 1.0, but neither was statistically significant (Table 3). Increasing IGF-2 levels were inversely and significantly associated with endometrial cancer, and the OR for the highest tertile was 0.35 (95% CI, 0.18–0.69).

Table 2. Selected descriptive factors for 174 cases and 136 controls

	Cases	Controls
	N	*N*
Age (yrs)		
<58	39	35
58–62	42	29
63–66	42	34
≥67	51	38
Race/ethnicity		
Non-Hispanic white	158	128
All other	16	8
Age at menarche (yrs)		
≥14	44	47
13	41	43
12	54	30
<12	33	15
No. of pregnancies		
0	29	15
1 or 2	56	38
3 or more	88	83
BMI (kg/m^2)		
<23.19	34	46
23.19–26.83	29	46
≥26.84	110	44
Current smoker?		
No	162	115
Yes	12	21
Waist-to-thigh ratio		
<1.7065	34	45
1.7065–1.914	40	43
≥1.915	90	43
Months of estrogen therapy		
0–4	149	127
4–59	12	7
≥60	12	2
Serum cholesterol (mg/dl)		
<214	77	44
214–255	53	46
≥256	40	45
Log albumin-bound estradiol (pg/ml)		
<0.076	35	45
0.076–0.76	33	45
≥0.77	103	45
Log serum hormone binding globulin (nM)		
<3.53	103	46
3.53–4.05	40	44
≥4.06	30	46
Serum C-peptide (ng/ml)		
<1.5	36	42
1.5–2.2	29	40
≥2.3	77	40

Table 3. Associations between endometrial cancer and IGF-1, IGF-2, IGFBP-1, and IGFBP-3[a]

	Cases	Controls	OR[b]	OR[c]	95% CI
IGF-1 (ng/ml)					
≤74.8	61	35	1.00	1.00	Ref
74.9–108.4	35	36	0.54	0.51	0.25–1.04
>108.4	46	34	0.89	0.63	0.30–1.32
IGF-2 (ng/ml)					
≤568	79	45	1.00	1.00	Ref
569–770	58	46	0.76	0.67	0.37–1.23
>770	37	45	0.50	0.35	0.18–0.69
IGFBP-1 (ng/ml)					
≤30.6	41	43	1.00	1.00	Ref
30.7–58.7	45	45	0.50	0.72	0.39–1.34
>58.7	85	44	0.45	1.04	0.50–2.14
IGFBP-3 (ng/ml)					
<3301.5	36	44	1.00	1.00	Ref
3301.6–3996.5	51	47	0.58	0.52	0.29–0.96
>3996.5	87	45	0.45	0.40	0.21–0.77

[a]Add numbers for excluded cases and controls.
[b]Adjusted for age, study site, and race.
[c]Adjusted for age, study site, race, log-SHBG, and BMI. 95% CI is for this OR.

In models adjusted for age, study site, and race, the highest tertile of IGFBP-1 was inversely associated with endometrial cancer. However, adjustment for SHBG and BMI—both individually and in combination—produced a null association. Higher IGFBP-1 was significantly associated with higher BMI and lower SHBG levels. The initial ORs for IGFBP-3 resembled the results for IGFBP-1, but fully adjusted ORs for increasing IGFBP-3 remained significantly below 1.00.

Although we recognized that some strata would contain small sample sizes, we explored the potential statistical interactions with BMI, SHBG, menopausal hormone therapy, and oral contraceptives. Only 33 and 46 participants had ever used menopausal hormones and oral contraceptives, respectively; restricting analyses to never-users produced no substantial change in the data. On the basis of median BMI and SHBG cutpoints, we saw no compelling evidence of stratum-specific associations. For IGF-1 and IGF-2, stratum-specific ORs were at or below 1.0, with the lone exception of the highest tertile of IGF-1 among women with SHBG above the median (OR = 1.46, 95% CI, 0.54–4.00). The inverse association with IGFBP-3 appeared in all BMI and SHBG strata.

Because IGFBP-3 binds most IGF-1 in serum, we evaluated the associations between endometrial cancer and the ratios of IGF-1 to IGFBP-3 and IGF-1 to IGFBP-1. Neither was significantly associated with endometrial cancer. The ORs for the highest ratio tertiles were 0.76 (95% CI, 0.36–1.62) for IGF-1 to IGFBP-3 and 0.47 (95% CI, 0.20–1.10) for IGF-1 to IGFBP-1.

We repeated the IGFs and IGFBPs analyses after excluding the 38 hysterectomy controls, but the results did not materially change. The associations for IGF-1, IGF-2, IGFBP-1, and IGFBP-3 were not dramatically changed after excluding the 45 women (32 cases and 13 controls) who had diabetes and the 1 case whose diabetes status was unknown (data not shown).

Discussion

This case-control study does not provide evidence that higher IGF-1 and IGF-2 levels are associated with an increased endometrial cancer risk in postmenopausal women. Instead, our data indicated that higher IGF-2 was inversely associated with endometrial cancer. The IGF-1 results differed from the IGF-2 data mainly in statistical significance, which could have arisen because the larger number of exclusions for our IGF-1 data decreased the statistical power of that particular analysis. Higher IGFBP-3 was also inversely associated with endometrial cancer. If a relative IGF excess, IGFBP deficit, or both, might facilitate endometrial proliferation and carcinogenesis, one would expect positive associations with elevated IGFs and inverse associations with elevated IGFBPs. Our data revealed the opposite for both IGF-1 and IGF-2 and an inverse association for IGFBP-3 but not IGFBP-1.

Two clinic-based studies directly evaluated circulating IGFs and IGFBPs in women with and without endometrial cancer, and some of their results mirror our data. One investigation that compared 32 endometrial cancer patients with 18 non-cancer patients noted lower IGF-1, IGF-2, and IGFBP-3 levels among cancer patients, but no difference in IGFBP-1 or IGFBP-2 (12). Another, of 23 patients and 27 hospital-based controls, reported higher IGF-1 but lower IGFBP-1 and IGFBP-3 in endometrial cancer patients (13). However, neither study included sufficient information about study population selection methods or distribution of potential confounders, and small sample size limited both studies.

Three studies since—an 84-case and 84-control study from Greece (14), a 288-case and 392-control study from Sweden (15), and a 166-case and 315-control study nested in cohorts from New York, Umea, Sweden, and Milan, Italy (16)—have more systematically analyzed IGFs, IGFBPs, and endometrial cancer. Adding our data to these reports reveals some patterns about potential associations with endometrial cancer. Analytic details slightly differed in the four studies, but each investigation used a generally accepted laboratory analysis and had roughly the same breadth and depth of other risk factor information available for multivariate modeling. All four reported ORs below 1.0 for higher IGF-1 levels, but only our data and a joint assessment of IGF-1, IGF-2, and IGFBP-3 in the Greek study (14) showed potentially strong inverse associations. That study was the only investigation other than ours to analyze IGF-2, and the two studies produced exactly opposite associations. IGFBP-1 generated null associations in our and the Swedish data (15) but an inverse association in the pooled nested case-control study (16). The IGFBP-3 data vary most substantially across the four studies: null associations in two studies (14, 15), a significant positive association in one, (16) and a significant inverse association here. To date, none of the epidemiological data supports the hypothesis that higher IGF-1 levels increase risk. The inconsistent data on IGF-2 and IGFBPs may reflect chance variation, true associations, or more complex relationships between insulin, the IGF system, and other endometrial cancer risk factors.

Despite the clear absence of an increased endometrial cancer risk among women with higher IGFs, steroid

hormones appear to influence IGFs and IGFBPs levels in the endometrium. Estrogens stimulate IGF-1 production and inhibit IGFBP-3 synthesis (7, 10, 11, 22), as does tamoxifen (23, 24). IGF-1 gene expression was higher in tissue taken from endometrial cancer patients than from women without endometrial cancer in two small studies (25, 26), and IGFs were shown to stimulate *in vitro* endometrial cancer cell growth (11). Progestins appear to increase IGFBP levels (2, 10, 27). The balance between IGFs and IGFBPs could influence endometrial cell proliferation similarly to the balance between estrogen and progesterone (7), but the IGFs system might also merely be a surrogate for steroid hormone activity (28).

Our IGFs and IGFBPs data should be interpreted in conjunction with other previous publications from this study, where endogenous estrogenic and androgenic hormones increased risk (3) but did not seem to completely explain the increased risk associated with higher body weight (6). In contrast, fasting C-peptide levels, which reflect insulin secretion, were only associated with endometrial cancer before statistical adjustment for BMI (17). The endogenous estrogens and androgen data are consistent with the unopposed estrogen theory, but our null associations with C-peptide and IGF-1, and the inverse association with IGF-2, do not support a direct additional role for ovarian hyperandrogenism and insulin (2). These null or inverse associations appeared in analyses performed with and without adjustment for serum estrogen levels and remained null or inverse after assessing potential confounders, which could indicate that IGFs are not mere surrogates for endogenous hormones. This issue, however, clearly warrants continued research, which would ideally occur in much larger studies that include prediagnostic and multiple sample collections.

This study's limitations deserve attention. First, as in many retrospective studies, we collected single biologic specimens for IGFs and IGFBPs analyses after the patients had been diagnosed with endometrial cancer. Our serum measurements could not address local IGF or IGFBP production in the endometrium. Second, although we reported acceptable CVs, the laboratory assay for IGF-1 displays considerable variability. After exclusion of two aberrant batches of IGF-1 results, the CVs were low, but other effects of measurement error are possible. Third, our statistical analysis did not include all of the original study participants because prior analyses had depleted all biological material for some participants. Unacceptably high coefficients of variation for IGF-1 measurements in two analytic batches (which we excluded) further reduced the sample size available for this analysis. Bias arising solely due to an association between IGF or IGFBP levels and the amount of serum consumed in prior analyses or lower volumes of donated serum seems unlikely, but each scenario is hypothetically possible. Major biases arising due to our exclusions also seem unlikely because (*a*) the risk factor associations (both for questionnaire data and serum hormones) in the current analytic population were nearly identical to those from our previous publications that used the larger study population, and (*b*) those risk factor associations did not differ in the included participants *versus* the excluded participants. Fourth, polycystic ovarian syndrome (PCOS) may unify a number of the risk factors investigated or discussed here (27), but we had minimal information on the diagnosis of PCOS among our study subjects; only two cases and six controls reported this condition (18). Finally, to strongly implicate one particular IGF or IGFBP in endometrial carcinogenesis would require a complete assessment of the IGFs system, which neither we nor the other recent studies have attempted.

In conclusion, higher IGF-1 levels were not associated with an increased endometrial cancer risk in postmenopausal women, and may be associated with a decreased risk. Higher IGF-2 and IGFBP-3 levels were associated with a decreased risk. The association between bioavailable IGF-1 and endometrial proliferation provides a potentially relevant mechanism for endometrial carcinogenesis, but our results and other recent studies provide no epidemiological support for the hypothesis that higher IGFs increase risk. Continued progress on the relationships between steroid hormones and the insulin system may help to identify crucial components of the endometrial cancer pathway that are potentially amenable to intervention.

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References

1. Key TJ, Pike MC. The dose-effect relationship between 'unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer, 1988;57:205–12.
2. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomark Prev, 2002;11:1531–43.
3. Potischman N, Hoover RN, Brinton LA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst, 1996;88:1127–35.
4. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer, 2001;84:975–81.
5. Austin H, Drews C, Partridge EE. A case-control study of endometrial cancer in relation to cigarette smoking, serum estrogen levels, and alcohol use. Am J Obstet Gynecol, 1993;169:1086–91.
6. Potischman N, Gail MH, Troisi R, Wacholder S, Hoover RN. Measurement error does not explain the persistence of a body mass index association with endometrial cancer after adjustment for endogenous hormones. Epidemiology, 1999;10:76–9.
7. Rutanen EM. Insulin-like growth factors in endometrial function. Gynecol Endocrinol, 1998;12:399–406.
8. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst, 2000;92:1472–89.
9. Rosen CJ, Pollak M. Circulating IGF-I: new perspectives for a new century. Trends Endocrinol Metab, 1999;10:136–41.
10. Liu HC, He ZY, Mele C, Damario M, Davis O, Rosenwaks Z. Hormonal regulation of expression of messenger RNA encoding insulin-like growth factor binding proteins in human endometrial stromal cells cultured *in vitro.* Mol Hum Reprod, 1997;3:21–6.
11. Kleinman D, Karas M, Roberts CT Jr, et al. Modulation of insulin-like growth factor I (IGF-I) receptors and membrane-associated IGF-binding proteins in endometrial cancer cells by estradiol. Endocrinology, 1995;136:2531–7.
12. Rutanen EM, Stenman S, Blum W, Karkkainen T, Lehtovirta P, Stenman UH. Relationship between carbohydrate metabolism and serum insulin-like growth factor system in postmenopausal women: comparison of endometrial cancer patients with healthy controls. J Clin Endocrinol Metab, 1993;77:199–204.

13. Ayabe T, Tsutsumi O, Sakai H, et al. Increased circulating levels of insulin-like growth factor-I and decreased circulating levels of insulin-like growth factor binding protein-1 in postmenopausal women with endometrial cancer. Endocr J, 1997;44:419–24.
14. Petridou E, Koukoulomatis P, Alexe DM, Voulgaris Z, Spanos E, Trichopoulos D. Endometrial cancer and the IGF system: a case-control study in Greece. Oncology, 2003;64:341–5.
15. Weiderpass E, Brismar K, Bellocco R, Vainio H, Kaaks R. Serum levels of insulin-like growth factor-I, IGF-binding protein 1 and 3, and insulin and endometrial cancer risk. Br J Cancer, 2003;89: 1697–704.
16. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP-1, -2 and -3 and risk of endometrial cancer. Int J Cancer, 2004;108:262–8.
17. Troisi R, Potischman N, Hoover RN, Siiteri P, Brinton LA. Insulin and endometrial cancer. Am J Epidemiol, 1997;146:476–82.
18. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol, 1992;167:1317–25.
19. Brinton LA, Hoover RN, Endometrial Cancer Collaborative Group. Estrogen replacement therapy and endometrial cancer risk. Unresolved issues. Obstet Gynecol, 1993;81:265–71.
20. Brinton LA, Barrett RJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD. Cigarette smoking and the risk of endometrial cancer. Am J Epidemiol, 1993;137:281–91.
21. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of ''untreated'' hyperplasia in 170 patients. Cancer, 1985;56:403–12.
22. Zhou J, Dsupin BA, Giudice LC, Bondy CA. Insulin-like growth factor system gene expression in human endometrium during the menstrual cycle. J Clin Endocrinol Metab, 1994;79:1723–34.
23. Kleinman D, Karas M, Danilenko M, et al. Stimulation of endometrial cancer cell growth by tamoxifen is associated with increased insulin-like growth factor (IGF)-I induced tyrosine phosphorylation and reduction in IGF binding proteins. Endocrinology, 1996;137: 1089–95.
24. Hung H, Pollak M. Regulation of IGFBP-3 expression in breast cancer cells and uterus by estradiol and antiestrogens: correlations with effects on proliferation: a review. Prog Growth Factor Res, 1995;6: 495–501.
25. Maiorano E, Loverro G, Viale G, Giannini T, Napoli A, Perlino E. Insulin-like growth factor-I expression in normal and diseased endometrium. Int J Cancer, 1999;80:188–93.
26. Rutanen EM, Nyman T, Lehtovirta P, Ammala M, Pekonen F. Suppressed expression of insulin-like growth factor binding protein-1 mRNA in the endometrium: a molecular mechanism associating endometrial cancer with its risk factors. Int J Cancer, 1994;59:307–12.
27. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc, 2001;60:91–106.
28. Smith GD, Gunnell D, Holly J. Cancer and insulin-like growth factor-I. A potential mechanism linking the environment with cancer risk. BMJ, 2000;321:847–48.